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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/593,639	12/29/2006	Lars Nilsson	1510-1121	4917

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EXAMINER	
CROUCH, DEBORAH	
ART UNIT	PAPER NUMBER
1632	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/593,639	NILSSON ET AL.	
	Examiner	Art Unit	
	Deborah Crouch	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *5,6,16-18,21 and 110* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-9,11-15,19,20,22 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/29/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Applicant's election with traverse of group IX, claims 1-4, 7-9, 11-15, 19, 20, 22 and 23 in the reply filed on January 15, 2009 is acknowledged. The traversal is on the ground(s) that the special technical feature is the production of a transgenic animal expressing a DNA sequence encoding β-amyloid that contains both the Artic mutation and another FAD mutation. Applicant argues the cited art does not teach this combination. Applicant further argues the Artic mutation is the first mutation found within the Aβ sequence, unlike the other FAD mutations that occur outside the Aβ sequence. Applicant argues the art does not suggest such a combination to produce an animal model. This is not found persuasive because applicant's assessment of a "special technical feature" is too narrow. MPEP 1893.03(d) states: "The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art." However, the claimed inventions do not provide to the art a contribution over the prior art. As evidenced by Chishti, transgenic mice expressing an APP sequence containing two FAD mutations was known in the art at the time of filing. The mice taught in Chishti express APP FAD mutations 717 and 670/671. This establishes at the time of filing transgenic mice models expressing a double FAD mutant APP were known in the art. Then, Nilsberth provides evidence that an APP comprising the Artic mutation caused in vitro the formation of amyloid fibrils. It is noted the Artic mutation is an FAD mutation, and this is regardless of the position of the mutation within the APP sequence. Thus the production of mice expressing a doubly FAD mutant APP DNA sequence was known at the time of filing, as was the DNA sequence encoding APP Artic. Considered as a

whole, the present claims are a substitution for that which was known in the art at the time of filing that is substituting an FAD APP-Artic DNA sequence for the FAD APP-670/671 DNA sequence in a mouse expressing an FAD APP-717 DNA sequence. For these reasons, the claimed invention lacks a special technical feature.

The requirement is still deemed proper and is therefore made FINAL.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 7-9, 11-15, 19, 20, 22 and 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse whose genome comprises a DNA sequence encoding a heterologous APP comprising the Arctic mutation (E693G) and a pathogenic AD mutation operably linked to a promoter or whose genome comprises a DNA sequence encoding a heterologous APP comprising the Arctic mutation (E693G) operably linked to a promoter and also comprises an second DNA sequence encoding a heterologous APP comprising a pathogenic AD mutation operably linked to a promoter, methods of making the mouse and methods of screening using the mouse, does not reasonably provide enablement for a transgenic nonhuman animal expressing a DNA sequence encoding APP-Arctic and any transgene affecting AD pathogenesis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Language used in the scope rejection can be found in the specification, page 4, lines 29-33, and elsewhere in the specification. The intent is to limit the claims to a transgenic mouse whose genome has integrated into its genome a transgene comprising a promoter in operable linkage to a DNA sequence encoding an APP comprising both the Artic mutation and another DNA sequence encoding an APP mutation associated with Alzheimer's disease, and a transgenic mouse whose genome has integrated into its genome a transgene comprising a promoter in operable linkage to a DNA sequence encoding an APP comprising the Artic mutation and a transgene comprising a promoter operably linked to a promoter a DNA sequence encoding an APP mutation associated with Alzheimer's disease. The APP mutations associated with Alzheimer's disease are those mutations occurring with the APP protein and are represented by mutations at amino acid positions 717, 670, 671. These mutations are not found in proteins encoded by separate genes such as presenilin or tau.

The claims presently being examined are drawn to a transgenic non-human animal expressing at least one transgene comprising a DNA sequence encoding a heterologous APP comprising at least the Arctic mutation (E693G) and a further AD pathogenic mutation or a further transgene affecting AD pathogenesis, which results in increased amounts of intracellular soluble Aβ aggregates, including Aβ peptides, methods of producing the animals and methods of screening for agents useful in treating, preventing or inhibiting Alzheimer's disease by administering selected agents to the animals.. However, for the reasons set forth below, the claims are not enabled for their full breadth.

The specification teaches the production of transgenic mice whose genomes comprise a DNA sequence encoding APP consisting of the Artic mutation (E693) and the Swedish mutation (MK670/671NL) by conventional pronuclear injection (Examples, page 17). The resulting Thy-SweArcAPP mice exhibit increased formation of Aβ aggregates as comprising Thy-SweAPP mice. While this disclosure is sufficient for transgenic mice, the scope as written to transgenic animals is not predictable given the art at the time of filing.

Rats are a particularly attractive mammalian species in which to model Alzheimer's disease, however, transgenic rats expressing an APP transgene have not been disclosed to develop Alzheimer's disease pathology or tau pathology. Echeverria states transgenic rats expressing APP-Swe K670N,M671L and Indiana V717F, with or without PS1 M146L were produced by co-injection of transgenes into rat fertilized eggs (Echeverria, page 210, col. 1, parag. 4). Transgenic rat lines UKRU25 (hemizygous for the App-Swe/Indiana transgene and the PS1 M146L transgene) and UKRU28 (homozygous for the APP-Swe/Indiana transgene) failed to produce extracellular amyloid deposits, that is the rats failed to produce plaques (Echeverria, page 216, col. 2, parag. 2, lines 1-7). The rats produced what are referred to as "preplaques" (Echeverria, page 217, col. 2, lines 4-9). This is in stark contrast to transgenic mice expressing APP Swe/Indiana transgenes. These mice exhibited ThioS positive fibrillar and non-fibrillar plaques, but at a much earlier age than other mice (Dudal, page 868, col. 1, parag. 1, lines 17-19 and parag. 3, lines 1-3). This phenotype did not appear at

all the transgenic rats of Echeverria. The mice showed microglia activation around the deposits, something that would occur in the transgenic rats, as microglia activation requires extracellular amyloid deposit formation (Dudal, page 868, col. 2, parag. 1). This is clear evidence that the phenotypes obtained in transgenic rats expressing APP transgenes are not predicted by the phenotypes obtained in transgenic mice expressing the same transgene. Therefore at the time of filing, the skilled artisan as being unpredictable would have regarded the production of the breadth "transgenic animals".

Further, the art at the time of filing taught that the production for breadth of transgenic animals is unpredictable due to silencing, copy number and modifications of the transgene. With regard to transgene integration the art teaches that the site of integration is uncontrolled and yet is critical due to the possibility of integration into a silent locus. The site of integration may also result in altered tissue specificity, although the promoter used behaves differently at its normal chromosomal localization, with neighboring regulatory elements potentially influencing the transcriptional activity of the transgene (Ristevski, pg. 159 col. 1 parag. 3 lines 1-7). This is known as chromosomal position effects, where host sequences surrounding the site of transgene integration can alter the expected expression pattern, turning it ectopic or not detectable (Montoliu, pg 39, col. 1). With regard to copy number the art teaches that controlling the transgene copy number (usually integration is a singular event with multiple copies integrated in tandem) is also problematic in the generation of transgenic animals (Ristevski, pg. 159 col. 1 parag. 3 lines 7-11). A high tandem copy number results in a gene silencing effect, and further, is undesirable if the effect of a gene dosage is being addressed, as

multiple copies will not recapitulate relevant levels of expression (Ristevski, pg. 159 col. 1 parag. 3 lines 11-14 bridge col. 2 parag. 1). The art provides that the production of transgenic animals in general is unpredictable because of uncontrollable phenomenon associated with the methodology.

Thus, at the time of the present invention the skilled artisan would have needed to engage in an undue amount of experimentation without a predictable degree of success to make and use the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14-21 are rejected under 35 U.S.C 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are microinjecting the transgene into a fertilized egg or an embryo, transferring to a surrogate mouse and term delivery. Also omitted are any steps related to rendering the endogenous APP non-expressive.

Claims 22 and 23 are rejected under 35 U.S.C 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are all of those related to the method of screening: administering an agent to an animal of claim 1; observing effects of the agent on the animal's ability to form Aβ peptides; comparing to a animal of claim 1 that did not received the agent; selecting as an agent for the treatment, prevention or

inhibiting Alzheimer's disease an agent that demonstrates a decrease in Aβ formation in the treated animal as compared to the untreated animal.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 7-9, 11-15, 19, 20, 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chishti et al. (2001) J. Biolog. Chem., pp. 21562-21570 in view of Nilsberth et al. (2001) Neurosci., Vol. 21, pp. 1444-1451, both IDS 12/29/06.

Chishti teaches the production of transgenic mice expressing double APP-FAD mutations, V717F and Swe using pronuclear injection (page 21564, col. 1, parag, 1, lines. 14-24). Chishti teaches the resulting TgCRND8 mice exhibited "potent deposition of cerebral amyloid," an enhancement over art known transgenic mouse models of Alzheimer's disease (page 21566, col. 2, parag. 1, lines 6-12). However, Chishti does not teach a double transgenic mouse expressing double APP-FAD mutations, one of which would be the Arctic mutation.

Nilsberth taught a DNA sequence encoding the APP-Arctic mutation (page 888, col. 1, parag.3). Nilsberth further demonstrates the formation of amyloid protofibrils in transfected HEK293 cells (page 888, col. 2, parag. 2, line 1 to page 889, col. 1, line 2). Media from cells transfected with the Arctic, Dutch or Italian mutation, each at amino

acid position 693, showed a 22-33% reduction in Aβ42/40 ratio (page 889, col. 1 lines 9-14) and Table 1). Decrease levels of Aβ42 seen in the media of the infected cells is in parallell with that known previously for the Dutch mutation (page 889, col. 1, parag. 2, line 5 to col. 2, line 10). Motivation is provided by Nilsberth teaching the Arctic mutation produces pathological disease through a mechanism of rapid Aβ protofibril formation different from the Dutch and Italian mutation, dementia versus vascular manifestation (page 892, col. 1, parag. 1, lines 3-8).

Thus at the time of filing, it would have obvious to the ordinary artisan to modify the teachings of Chishti by substituting a DNA sequence encoding APP-Arctic for either APP-717 or APP-Swe to produce a transgenic moue expressing a DNA sequence encoding APP-Artic and a second APP-FAD mutation to determine the mechanism of APP-Arctic pathology.

The combination of prior art cited above in all rejections under 35 U.S.C. 103 satisfies the factual inquiries as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Once this has been accomplished the holdings in KSR can be applied (*KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. ___, 82 USPQ2d 1385 (2007): "Exemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) "Obvious to try" - choosing from a

finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention." In the present situation, rationales A, B, E, F and G are applicable. The claimed method was known in the art at the time of filing as indicated by the cited prior art. Thus, the teachings of the cited prior art in the obviousness rejection above provide the requisite teachings and motivations with a clear, reasonable expectation. The cited prior art meets the criteria set forth in both Graham and KSR.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Fri, 6:00 AM to 3:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Deborah Crouch/
Primary Examiner, Art Unit 1632

April 14, 2009